Project Details	
Project Code	NMH27Ba Lancaster
Title	The brain-skin link in psychosis: uncovering shared biology and new treatment targets
Research Theme	Neuroscience & Mental Health
Project Type	Dry lab
Summary	Severe mental illnesses (e.g. schizophrenia/bipolar disorder) affect the whole body, not just the brain - and share genetic links with inflammatory conditions, including acne, a common long-term skin condition. However, we still do not fully understand these links - how they work biologically, or what they might mean for treatment. The candidate will join a leading UK mental health research network (Brain & Genomics UKRI Mental Health Platform) to study how shared genetic risk between psychosis and acne affects brain health and symptoms, and to identify new treatment targets. This work will reveal new biological pathways and potential drug targets.
Description	Background: Psychotic disorders (such as schizophrenia and bipolar disorder) and skin conditions (such as acne vulgaris), commonly co-occur in the population and may share pathophysiological mechanisms. While there are substantial polygenic contributions to psychosis strongly implicating a genetic architecture within the central nervous system/synaptic biology, there is considerable overlap with disorders of systemic inflammation, including acne vulgaris, a common chronic inflammatory skin condition (PMID:35132056). Individuals with acne vulgaris are also up to three times more likely to experience suicidal ideation and other psychiatric disorders than those with little or no acne (PMID: 20844551) suggesting this comorbidity could shape clinical outcomes. This shared aetiology implicates risk factors beyond brain tissue, co-implicating developmental and cellular signalling pathways that could be explored for increased mechanistic understanding and therapeutic benefit. The genetic overlap is driven by shared liability at several loci, such as the FADS1/2 gene cluster, DLG1 and RERE loci, implicating lipid metabolism and synaptic organisation (PMID:41639594) and retinoic acid signalling respectively. The relationship between retinoid-based acne treatments and psychiatric outcomes is still being investigated, and genetic liability to schizophrenia has also been linked to differences in vitamin-A–related pathways, including biochemical precursors of retinoic acid (PMID: 31666680). There is also emerging evidence for a role of DRD2 signalling in the skin, raising the possibility that dopaminergic dysfunction linked to psychosis risk could have dermatological consequences. Little is known about how this shared biology influences brain health, disease severity and treatment responses. These observations warrant further characterisation of the shared aetiology between psychosis and inflammatory skin disorders, to better understand how psychiatric illnesses link to inflammatory processes, explore the impact of co-morbidity and will develop our understanding of heterogeneity across the psychosis spectrum. Last, the project has the potential to uncover novel therapeutic targets acting across a brain–skin axis for personalised treatments. Key Research Questions and Objectives: How does shared genetic liability between psychosis and acne vulgaris influence biological

	pathways, brain health, and clinical trajectories, and can these mechanisms be leveraged to identify actionable therapeutic targets? Objective 1) Understand shared neurobiology: Quantify the extent/specificity of shared genetic architecture between psychosis and acne vulgaris using a range of bioinformatic approaches. This will include the identification of shared i) polygenic and b) causal variants and their enrichment within specific tissues/cell types (for example, neuronal sub-types/peripheral cutaneous neurons) and using approaches such as co-localisation, cell-type-specific & data-driven clustering approaches (PMIDs:36749789;32915962;41207220). Objective 2) Identify clinical/neurobiological correlates. The candidate will leverage this shared genetic aetiology as well as e-health record data and immune-profiling data to assess how acne vulgaris genetic risk, biomarkers or diagnosis correlate with clinical symptom and neuroimaging-derived metrics of brain health as part of The Bipolar, Schizophrenia, and Psychosis Research Initiative of the Brain and Genomics Hub (B-SPRINT) study, a 600+ cohort of individuals experiencing psychosis. This will enable the identification of clinically meaningful subgroups that reflect underlying shared biology, supporting improved stratification and the development of biologically informed biotypes. Ethical approval for the B-SPRINT has been established (Wales REC 7 (25/WA/0027)) and data collection is due to be finalised during the proposed PhD (Early 2028). Objective 3) Drug-target proxies via Mendelian randomisation: The candidate will evaluate causal relationships between biologically relevant drug targets and acne/psychosis risk using Mendelian randomisation. Protein quantitative trait loci, derived from exposures like UK Biobank Pharma Proteomics Project, with acne vulgaris and psychosis GWAS modelled as outcomes. Here, we will explore genetic proxies for psychosis using atypical antipsychotic exposure and acne vulgaris treatments such as protein targets for tetracycline antibiotics and retinoids. Student Ownership: This project will attract individuals from a range of academic backgrounds, including psychology/neuroscience/biostatistics/molecular biology/immunology/dermatology. We will capitalise on student's prior expertise/training to develop and enhance specific areas of the project and encourage and support the application of prior experience in the context of the project. For example, we would be interested in input from a psychology student to best operationalise clinical symptom data and would encourage a review/pilot study exploring how acne vulgaris links to specific clinical symptom features in existing datasets to generate hypothesis for our patient-oriented Brain & Genomics hub of the Mental Health Platform. To support students without a data science/biostatistics background, training will be provided by the supervisors in the R environment with toy data sets of scaled complexity and via GW4-led courses/workshops to ensure comprehensive skill development. We would further encourage/promote exercises using open-access datasets to develop skillsets that enhance the agency/confidence of the candidate to work in a proactive and independent manner. An example of this would be establishing positive controls for the drug-proxy MR studies (such as using IL6 / C-Reactive

	Protein SNP instruments as genetic drug proxy for Tocilizumab for inflammatory conditions like Rheumatoid Arthritis). Similarly, we would encourage/cultivate enthusiasm for any facet of data dimension (genetics, blood-based markers, p/s/e/m/QTL data) that can be supported by the supervisory team.
Can be completed part time?	Yes
Supervisory Team	
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